The University of Chicago

I. THE PREPARATION OF ALDONIC AND SACCHARINIC ACID AMIDES IN LIQUID AMMONIA

II. LACTONES IN LIQUID AMMONIA

A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1936

By

DUNCAN MACMILLAN

Private Edition, Distributed by
THE UNIVERSITY OF CHICAGO LIBRARIES
CHICAGO, ILLINOIS

Reprint from the Journal of the American Chemical Society, 56, 2481 (1934) and 58, 898, (1936)

The University of Chicago

I. THE PREPARATION OF ALDONIC AND SACCHARINIC ACID AMIDES IN LIQUID AMMONIA

II. LACTONES IN LIQUID AMMONIA

A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
1936

By
DUNCAN MACMILLAN

Private Edition, Distributed by
THE UNIVERSITY OF CHICAGO LIBRARIES
CHICAGO, ILLINOIS

Reprint from the Journal of the American Chemical Society, 56, 2481 (1934) and 58, 898, (1936)

ACKNOWLEDGEMENT

The author wishes to thank Dr. J. W. E. Glattfeld, under whose guidance this research was done, for his unfailing interest and encouragement, and Dr. W. C. Johnson and Dr. A. E. Sidwell, Jr., for technical assistance and advice.

R. UNIV.
BIBLIOTHEEK
LEIDEN

The Preparation of Aldonic and Saccharinic Acid Amides in Liquid Ammonia

By Duncan Macmillan

The desirability of obtaining erythrose in its optically active as well as inactive forms has been mentioned recently.[1] These tetroses are needed in order to make possible certain plans for a study of the conversion of the tetroses into the C_4-saccharinic acids. At the present time these sugars are not available in pure condition and efforts are being made in this Laboratory to produce *dl*-erythrose by the reduction of *dl*-erythronic lactone. The methods of reduction so far tried, when applied to *dl*-erythronic lactone, have not produced the tetrose. These experiments were carried out practically entirely in aqueous solution. It seemed desirable to try the reduction of the lactone also in other media, and liquid ammonia was therefore used. These reduction experiments in liquid ammonia led at once to the new procedure for the preparation of the amides that is reported below.

Very little work has been done so far with the carbohydrates or their derivatives in liquid ammonia. The most recent work reported in the literature along this line is that of Muskat.[2] This author apparently did not work with the sugar acids, however, and was interested especially in the alkylation of the sugars.

Amides of aldonic and saccharinic acids have been prepared in a number of ways, such as the solution of the lactones in aqueous ammonia,[3] the treatment of alcoholic solutions with ammonia gas,[4] and the hydrolysis of nitriles.[5] As amide formation in liquid ammonia proceeds rapidly, and requires little apparatus, the new method has some advantages over those previously employed. Thus several attempts to obtain *dl*-erythronamide by the procedure described by Weerman[4] were made. In each case the product was a gum which would not crystallize even when subjected to scratching, cooling, evacuation or trituration. The liquid ammonia technique was then used, and the resulting gum crystallized on standing in a vacuum desiccator. Also in the preparation of certain amides, in which it is otherwise necessary to work with absolute alcohol in anhydrous systems, the liquid ammonia technique is far more convenient.

While all aldonic and saccharinic acid lactones used so far have yielded amides at liquid ammonia temperatures, this is not true of some other lactones. For example, it is found that coumarin may be recovered from liquid ammonia unchanged. The lactone of γ-hydroxybutyric acid is not affected by liquid ammonia at its boiling point, although it is ammonolyzed at room temperature when sealed in a bomb with liquid ammonia. An extended study of ammonolysis of lactones is under way, and it is hoped that it may lead to a further understanding of the lactone bond.

(1) Glattfeld and Forbrich, *J. Am. Chem. Soc.*, **56**, 1209 (1934).
(2) Muskat, *ibid.*, **56**, 693 (1934).
(3) Hudson and Komatsu, *ibid.*, **41**, 1141 (1919).
(4) Weerman, *Rec. trav. chim.*, **37**, 24 (1918).
(5) Kiliani, *Ber.*, **19**, 3033 (1886).

Experimental Part

The reaction may be carried out in the type of apparatus described by Fernelius and Johnson[6] in their review of the liquid ammonia system. It is not necessary, however, to use anhydrous conditions. The results are thoroughly satisfactory when an open Dewar flask is used or when the lactone is dissolved in the liquid ammonia in an open dish. Owing to the great solubility of carbohydrate derivatives in liquid ammonia, comparatively little ammonia is required. The author's practice has been to dissolve between 15 and 30 g. of lactone in about 300 cc. of liquid ammonia in an open Dewar flask. The reaction is usually complete in a few hours. Completion may be hastened by pouring the solution into an evaporating dish. In general the amide crystallizes as soon as the liquid ammonia has evaporated. The yields of ammonia-free residue are quantitative. The following description is typical of the procedure.

The Preparation of *d*-Gluconamide.—Seventeen and eight-tenths grams (0.1 mole) of *d*-glucono-γ-lactone (m. p. 133°) was dissolved in 300 cc. of liquid ammonia in an evaporating dish. A stream of warm air was passed over the surface of the solution. Within an hour the ammonia had evaporated, leaving a residue which was pumped free of ammonia in a vacuum desiccator. The solid residue melted at 139–140°, and decomposed at 142°. The weight was 19.4 g., corresponding closely to that of 0.1 mole of gluconamide (19.5 g.). The amide was then recrystallized from 300 cc. of 90% alcohol. The recrystallized substance melted at 143–144° and weighed 15.5 g.

No difficulty was experienced in using this procedure in the preparation of all amides reported below except that it proved difficult to obtain the erythronamides in crystalline form from the residual gums at first. When crystal seeds were once available, however, this difficulty disappeared. All other residues from the evaporation of the ammonia crystallized easily.

The new compounds were analyzed for nitrogen. Only a small amount of *d*-erythronamide that had been used for rotations was available for the analysis. This may account for the low value.

TABLE OF THE CONSTANTS AND ANALYSES OF SOME OF THE AMIDES PREPARED IN THE COURSE OF THIS WORK

The specific rotations of the galactonamide and the mannonamide made by the new procedure were considerably different from those reported in the literature.[3] These amides were therefore made by the Weerman method also and the constants found to be the same as those of the amides made by the new procedure. New compounds are marked with asterisks. All rotations were taken in water solution at the concentration shown in the last column and at "room temperature" (approximately 20°).

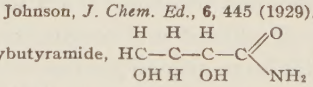
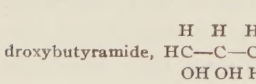
Name	M. p., °C.	$[\alpha]_D^{20}$	Concn., %	Formula	Kjeldahl nitrogen, % Calcd.	Found	
**dl*-1,3-Dihydroxybutyramide[7]	118.5–119.5			$C_4H_9O_3N$	11.76	11.77	11.66
**dl*-2,3-Dihydroxybutyramide	90.7			$C_4H_9O_3N$	11.76	11.69	11.65
**dl*-Erythronamide	62.3			$C_4H_9O_4N$	10.37	10.28	10.30
**d*-Erythronamide	94.8	+28.2	4.8	$C_4H_9O_4N$	10.37	9.74	
**l*-Erythronamide	94.8	−28.0	5.1	$C_4H_9O_4N$	10.37	10.55	
d-Galactonamide	175.0	+31.5	3.8				
d-Galactonamide (Weerman method)	176.0	+31.8	1.8				
d-Gluconamide	145.0	+31.0	5.0				
d-Mannonamide (from γ-lactone)	176.0	−13.1	2.2				
d-Mannonamide (from δ-lactone)	177.0	−13.1	3.0				
d-Mannonamide (by Weerman method)	176.0	−13.2	2.7				

Summary

The author has developed a simple method for the preparation of the amides of the aldonic and saccharinic acids which consists essentially of the solution of the lactones of the acids in liquid ammonia.

The preparation of *dl*-1,3-dihydroxybutyramide, *dl*-2,3-dihydroxybutyramide, *d*, *l* and *dl*-erythronamide is reported for the first time.

(6) Fernelius and Johnson, *J. Chem. Ed.*, **6**, 445 (1929).

(7) 1,3-Dihydroxybutyramide,  ; 2,3-dihydroxybutyramide,  .

Lactones in Liquid Ammonia

DUNCAN MACMILLAN

In an earlier article[1] the author described the preparation of aldonic and saccharinic acid amides in liquid ammonia. In the procedure employed

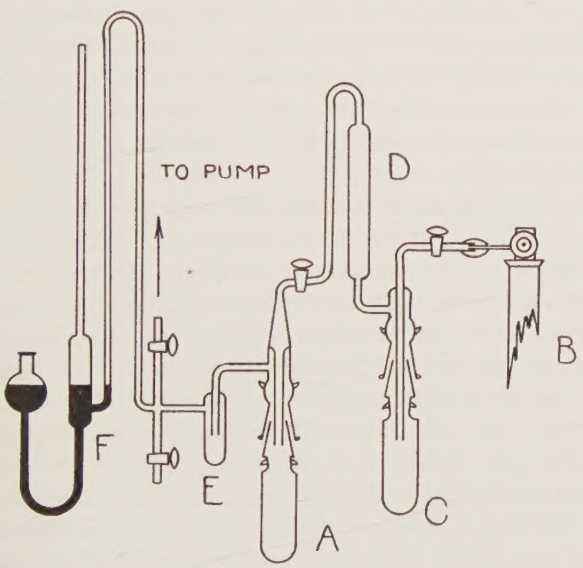


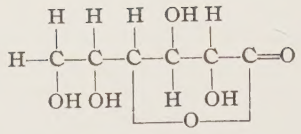
Fig. 1.

it was found that the lactones of sugar acids were readily ammonolyzed and gave quantitative yields of the amides. Experiments with lactones of the other types indicated that not all lactones show this property. This suggested that further study might contribute to an understanding of the lactone bond. It seemed desirable that the work be done on a quantitative basis, and under anhydrous conditions. For this purpose a system capable of evacuation was constructed, as shown in the figure.

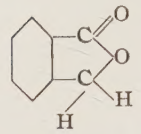
Since the same procedure was used in all cases, a general description may be given. A quantity of the material to be studied was placed in a weighed tube (A), the open end of which was the inner cone of a ground-glass joint; the joint was greased and the tube placed in the line. The system was evacuated to a pressure of 10^{-4} mm. with a mercury vapor pump. The tube was then detached, the joint cleaned with ether, and the tube weighed, after which it was again placed in the line and evacuated. Ammonia was then condensed from a small tank (B) into a tube (C) which contained sodium metal, over which the ammonia was allowed to stand until the blue color became permanent. The ammonia was then distilled through a column (D) packed with glass wool, into the reaction tube (A). The purpose of the glass wool was to remove small amounts of

(1) Glattfeld and Macmillan, *J. Am. Chem. Soc.*, **56**, 2481 (1934).

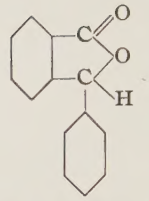
TABLE I



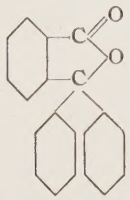
d-Glucono-γ-lactone



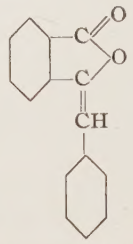
Phthalide



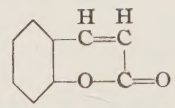
3-Phenylphthalide



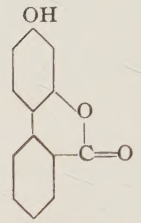
Phthalophenone



3-Benzalphthalide



Coumarin



Lactone of 2′,4′-dihydroxydiphenyl-2-carboxylic acid

Substance	Initial wt., g.	Final wt., g.	Calcd. for lactone + 1 NH_3
d-Glucono-γ-lactone	0.8878	0.9723	0.9726
Phthalide	.0408	.0402	
3-Phenylphthalide	.1010	.1006	
Phthalophenone	.2655	.2642	
3-Benzalphthalide	.3337	.3582	.3593
Coumarin	.0428	.0425	
Lactone of 2′,4′-dihydroxydiphenyl-2-carboxylic acid	.0456	.0461	

sodium or sodium amide which might have been carried over, a complication which has occurred in other work in these laboratories.

In general, if the material dissolved readily the ammonia was removed soon after solution was complete. This was done by condensing it in the trap (E). If the material did not dissolve readily the mixture was allowed to stand for several hours. The vacuum pump was applied as soon as the ammonia had been distilled into the trap (E), except in some of the experiments with the phthaleins, in which it was necessary to know the weight of the material very soon after treatment with ammonia. In the latter case the ammonia was allowed to boil out of the trap through the blow-off tube (F). Pumping was continued until the system had returned to its initial pressure, after which the tube was detached, cleaned and weighed. In all experiments save those with the phthaleins, the original pressure and a constant weight were reached in a few hours; in the phthalein experiments constant weight was not reached until many weeks had passed. In Table I are shown the results of the experiments on a number of lactones.

It will be seen from the data that, as was stated in the earlier article, *d*-glucono-γ-lactone is completely ammonolyzed, but that, of the other lactones investigated, only one, benzal phthalide, is ammonolyzed. The product obtained in the last case melted at 164–165°, and was, therefore, the amide of desoxybenzoin carbonic acid, $C_6H_4(CONH_2)(COCH_2C_6H_5)$, prepared originally by Gabriel[2] formed presumably by the opening of the lactone ring and not by the absorption of ammonia at the ethylene linkage of benzal phthalide.

Because acid lactones are regarded as intramolecular esters the behavior in ammonia of some simple esters was studied. Due to the volatility of the esters the vacuum technique did not lend itself to the work, and the experiments were carried out in a reaction tube of the type described by Fernelius and Johnson.[3] The results are of a qualitative nature. Esters ammonolyzed by liquid ammonia at its boiling point are methyl, ethyl, propyl and butyl lactates, ethyl mandelate and ethyl phenyl acetate. Esters not ammonolyzed under the same conditions as above are butyl acetate, ethyl benzoate, methyl salicylate and glycerol monoacetate. It is interesting to note that, while the lactones studied have been

(2) Gabriel, *Ber.*, **18**, 2434 (1885).

(3) Fernelius and Johnson, *J. Chem. Ed.*, **6**, 445 (1929).

TABLE II

Substance	Wt. before soln., g.	Wt., g., after		Calcd. for Subst. +	G.
Phenolphthalein I	0.1062	1 hour	0.1113	1 NH_3	0.1119
Phenolphthalein II	.4615	3 hours	.4886	1 NH_3	.4862
Phenolphthalein III	.2173	1 week	.2206	1 NH_3	.2289
Phenolphthalein IV	.2711	1 month	.2726		
		1.5 months	.2722		
		4 months	.2717	1 NH_3	.2856
Phenolphthalein V	.1436 +	5 weeks	.1446		
	NH_4NO_3 .7598				
Fluorescein I	.1930	20 hours	.2103	1 NH_3	.2092
Fluorescein II	.2199	1 month	.2315		
		4 months	.2300	1 NH_3	.2883
Maleinfluorescein	.2094	1 hour	.2432	3 NH_3	.2474
		1 month	.2312		
		3 months	.2282	1 NH_3	.2221

either quantitatively ammonolyzed or not ammonolyzed at all, the reaction is often incomplete in the case of the esters. For example, the lactates were ammonolyzed to the extent of 30–50%. The combined data of the present and preceding articles indicate that oxygen atoms bound to carbon atoms within the ring weaken the lactone bond.

Since phenolphthalein and fluorescein are lactones related to phthalide, their behavior in liquid ammonia was also studied. The results of the experiments were entirely different from those of the other lactones investigated. In general it may be said that phenolphthalein and fluorescein add ammonia, but the data indicate that definite, stable compounds are not formed. A gradual loss of the added ammonia continues for several weeks before constant weight is reached. To demonstrate that this property of gradual loss of ammonia is not shared by ammonia derivatives of similar compounds, ammonium benzoate and the amide of desoxybenzoin carbonic acid were kept in evacuated tubes in the line for periods comparable with those required for complete loss of ammonia by the phthaleins. A sample of ammonium benzoate of which the initial weight was 0.4899 g. weighed 0.4903 g. after five weeks. A sample of the amide of desoxybenzoin carbonic acid of which the original weight was 0.1848 g., weighed 0.1840 g. after four weeks.

The case of phenolphthalein is more clear cut than either of the others, and it may be worth while to describe its behavior in some detail. Phenolphthalein dissolves in liquid ammonia giving an intensely purple solution, the color of which shows no tendency to fade. When the ammonia is removed a red residue is obtained. As pumping is continued, the color fades to a bright pink which seems permanent. Prolonged evacuation finally brings the compound very close to the original weight of phenolphthalein. This final residue has a very strong tendency to absorb moisture from the air, a property which dry phenolphthalein does not have. While a quantitative analysis of the residue for carbon and hydrogen was made difficult by this property, analysis for nitrogen showed that none was present. The exact nature of the pink compound is not known. Heating discharges the color, and the compound melts at the melting point of phenolphthalein.

Gibbs[4] treated phenolphthalein with methylamine under conditions similar to those described in this work, and obtained a white compound to which he gave the formula $C_6H_4C_2O_2(C_6H_4ONH_3CH_3)_2$. Dehn[5] prepared a colorless ammonium salt by treatment of phenolphthalein with aqueous ammonia. The pink material obtained in the present research is apparently not analogous to either of these substances, but seems to be, rather, another form of phenolphthalein which is deposited in an ammoniated condition.

Summary

The author has continued his study of the ammonolysis in liquid ammonia of the lactone bond. The lactones studied were either completely ammonolyzed or not ammonolyzed at all.

(4) Gibbs, *J. Am. Chem. Soc.*, **28**, 1405 (1906).
(5) Dehn, *ibid.*, **54**, 2947 (1932).

All those which were not ammonolyzed had no hydroxyl group attached to a carbon atom in the lactone ring. Phenolphthalein is temporarily ammonolyzed but the product formed loses its ammonia completely on prolonged evacuation.